STUDIES IN THE AROMATIC HALOGENO-COMPOUNDS

by

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University of Edinburgh.

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C O N T E N T S.

OBJECT OF RESEARCH.

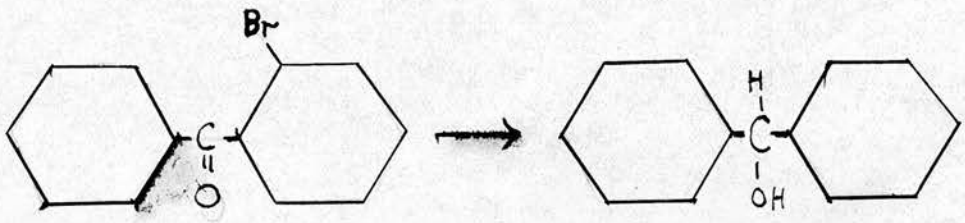
It was intended to investigate the method discovered by Campbell and Muir (unpublished) for removing halogen from aromatic halogen compounds by heating in a sealed tube with cuprous cyanide, pyridine and water. It was realised, when the work was still in the preliminary stages, that the apparatus available was unsuitable. Owing to war conditions, suitable apparatus was not readily available. A new furnace was not obtained until April 1945, when only a few weeks were left in which to complete the work. This investigation was therefore abandoned *pro tempore* and attention was turned to the synthesis of halogenophenylacetic acids and their derivatives.

INTRODUCTION.

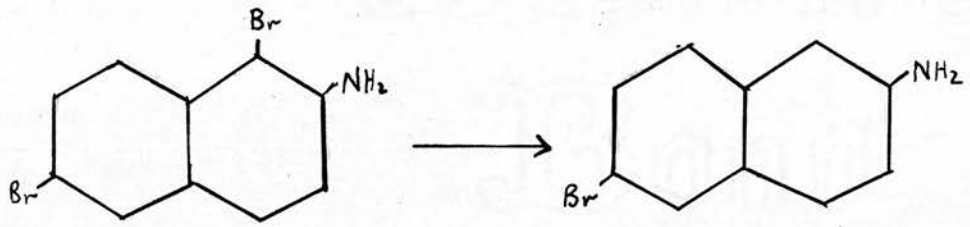
REMOVAL OF HALOGEN FROM AROMATIC HALOGENO-COMPOUNDS.

While the replacement of halogen by hydrogen is easily accomplished by the use of reducing agents such as hydriodic acid or hydrazine (e.g. Cox, Macbeth, and Pennycuick: J.C.S., 1931, 1870) in the case of aliphatic compounds and aromatic compounds with halogen in the side chain, the replacement of nuclear halogen generally requires more drastic conditions though there are cases scattered through the literature of halogen removal under comparatively mild conditions. For example, Klages and Liecke (J. Pr. Chem., 1900 [2] 61, 307) showed that 1-iodonaphthalene yielded naphthalene when boiled with hydriodic acid whereas the 2-compound was unchanged under the same conditions.

The presence of certain functional groups in a molecule often facilitates removal of halogen. Montagne (Ber., 1916, 49, 2243) showed that in bromobenzophenones bromine is removed when heated with alcoholic potassium hydroxide only if the bromine is ortho or para to the carbonyl group.



Amino and hydroxyl groups have a similar effect. Franzen and Stauble (J. Pr. Chem., 1921, [2] 101, 58) showed that 1-bromine was readily removed from polybromo-2-naphthylamines by the action of tin and hydrochloric acid; the bromine in 2:4-dibromo-1-naphthylamine is completely removed (J. Pr. Chem., 1922, [2] 103, 352). Similarly, in the polybromo-2-naphthols 1-bromine is removed by tin and hydrochloric acid or stannous chloride and hydrochloric acid.



Nicolet and co-workers (J.A.C.S., 1921, 43, 2081; 1927, 49, 1796, 1801, 1810) showed that halogen ortho or para to amino or hydroxyl was readily removed by hydrochloric acid or, better, stannous chloride and hydrochloric acid, the halogen being replaced by hydrogen. This method was used by Evans and Sandin (J.A.C.S., 1939, 61, 2916) for determining the position of double bonds in the naphthalene, hydrindene and tetralin nuclei.

Schwenk, Papa, Whitman and Ginsberg (J. Org. Chem., 1944, 9, 1) found that halogen in a large number of organic compounds could be removed quantitatively by reduction with Raney nickel alloy in aqueous alkali. Schwenk, Papa and Ginsberg (Ind. Eng. Chem. Anal., 1943, 15, 576) describe the application of this to the estimation of halogen in organic compounds.

Funke and Ristic (J. Pr. Chem., 1936, [2] 146, 151) obtained 2-ethyl-chrysene by Clemmensen reduction of x-bromo-2-acetyl-chrysene.

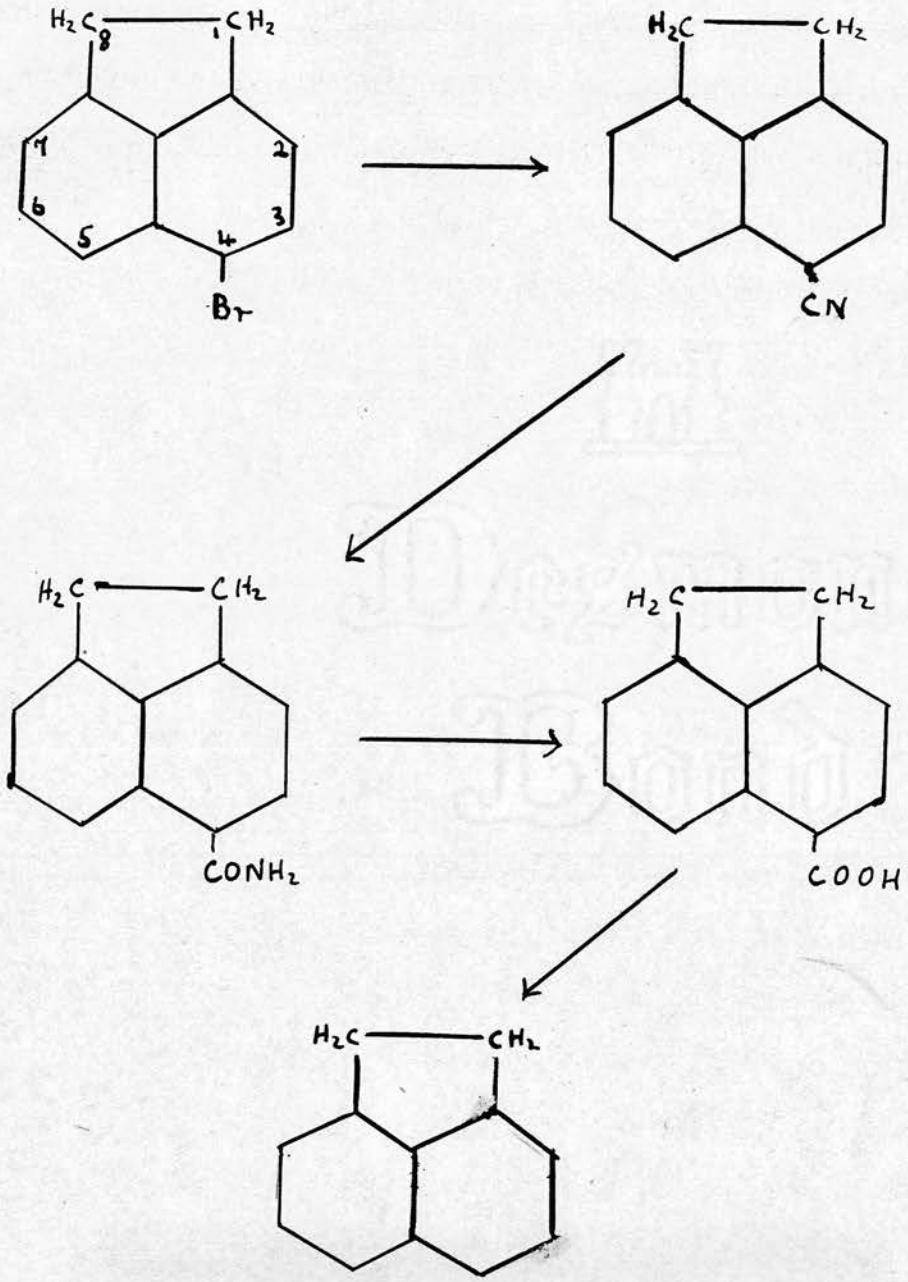
Catalytic hydrogenation using palladised calcium carbonate has been used to estimate halogen in organic compounds (Busch and Stöve, Ber. 1916, 49, 1063). Lesslie and Turner (J.C.S., 1932, 281) failed to obtain any diphenyl derivatives by the reaction of ethyl-2-chloro- and 2-bromo3:5-dinitrobenzoates and 1-iodo-tetrahydronaphthalene with copper bronze but obtained instead ethyl 3:5-dinitrobenzoate. Picryl chloride in boiling tetralin with copper bronze gave sym-trinitrobenzene obtained as the molecular compound with naphthalene, formed by dehydrogenation of the tetralin. It is well known that the halogen in 2:4:6-trinitrochlorobenzene and 3:5-dinitro-2-halogeno-benzoic esters is labile.

In an attempt to prepare halogeno-phenylacetoni-

triles by hydrogenation of mandelonitrile benzoates using the method of Kindler (v.i.) it was found that with o-chloromandelonitrile benzoates no hydrogenation of the ester group occurred but that instead the chlorine was removed as hydrogen chloride.

The above refers to the replacement of nuclear halogen by hydrogen. Other groups, however, can replace halogen in the aromatic nucleus; e.g. it can be replaced by the cyano group by the Rosenmund-von Braun reaction (Rosenmund and Struck, Ber., 1919, 52, 1749; von Braun and Marz, Ann., 1931, 488, 111; cf. Koelsch and Whitney, J. Org. Chem., 1941, 6, 795). In this reaction the halogeno-compound is heated with cuprous cyanide and pyridine at 200°.

It was surprising when it was established (Muir and Campbell, 1939) that, at a temperature higher than that generally used (280° instead of 200°) and with addition of water the product was not the acid or nitrile, as expected, but the parent hydrocarbon. It was decided to investigate this reaction further, with a view to establishing the mechanism. The halogeno-compound chosen for the investigation was 4-bromo-acenaphthene. A possible mechanism for the reaction was:


H2C
CH2
8
1
7
2
6
3
5
4
Br
CN
CONH2
COOH

The catalytic effect of copper on the decarboxylation of aromatic carboxylic acids is well known, though the examples are scattered through the literature and there has been very little systematic investigation of the effect. The use of pyridine, quinoline and high boiling tar bases as solvents with various copper catalysts has been found to facilitate the reaction.

DECARBOXYLATION.

Since an important step in the mechanism proposed for the removal of halogen by the above method is the decarboxylation of the acid formed by hydrolysis of the nitrile an investigation was made into the conditions under which aromatic carboxylic acids are decarboxylated. A general method, applicable to carboxylic acids, used both in preparative and qualitative organic chemistry, is to heat the acid or its sodium salt with soda-lime. There are other methods, however, which involve the use of less drastic reagents, and in some cases decarboxylation occurs readily when the acid is merely heated at or above its melting point, e.g. picolinic, quinaldinic and isoquinaldinic acids. Bistrzycki and Przeworski (Ber., 1912, 45, 3489) found that benziminazole-2-carboxylic acid lost carbon dioxide when heated at its m.p. (169°) giving benziminazole. Gilman, Janney and Bradley (Iowa State College J. Sci., 1933, 7, 429) found that certain furoic acids decomposed at temperatures between 100° and 250°. Hammick and co-workers (J.C.S., 1937, 1724; 1939, 809) have shown that when picolinic, quinaldinic and isoquinaldinic acids are decarboxylated by heating with aldehydes or ketones, substituted carbinols are formed, but when other acids that do not

contain the grouping -N=C(H)-COOH are used no carbinols are obtained.

$$R-C(=O)-O^- + H^+ \rightarrow R^- + CO_2 + H^+$$

$$R_1R_2CO + R^- + H^+ \rightarrow R_1R_2C(R)OH$$

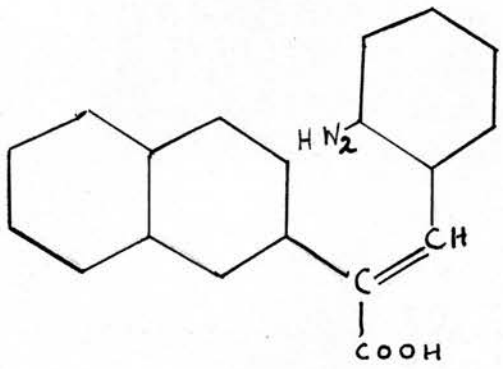
Kupferberg (J. Pr. Chem., 1877, [2] 16, 441) found that the methylamine and aniline salts of o- and p-hydroxy-benzoic acids on heating gave phenol whereas the salt of the m-hydroxy acid gave no phenol. Staudinger (Ber., 1906, 39, 3067) obtained fluorene by heating the quinoline salt of fluorene-9-carboxylic acid. Further work illustrating the catalytic effect of bases can be found in the following papers: Hemmelmayer, Monatsh., 1913, 34, 365; Claisen, Ann., 1913, 401, 21; 1917, 418, 71; Becker and Bistrzycki, Helv. Chim. Acta., 1919, 2, 111; Skita and Wulff,

Ann., 1927, 455, 24; Langenbeck and Hutschenreuter, Z. anorg. allgem. Chem., 1930, 188, 1; Bokland, Biochem. Z., 1930, 226, 56; Franke and Brathuhn, Ann., 1931, 487, 1; Rinkes, Rec. Trav. Chim., 1937, 56, 1142; Rodianov and Fedorova, Chem Abs., 1939, 33, 7296; 1941, 35, 2488; 1942, 36, 1032.

Various metals have been used for decarboxylating acids (cf. Meyer, Analyse und Konstitutionsermittelung organischer Verbindungen, 6th edn., p. 474) but the most successful is copper. Copper bronze and copper salts have been used either alone or with organic bases.

Diesbach and Bulliard (Helv. Chim. Acta., 1924, 7, 618) in attempting to prepare benzophenone-2:3':4'-tricarboxylic acid found that 4'-methyl-3'-chloro-bensophenone-2-carboxylic acid when heated with cuprous cyanide and pyridine at 200° gave 4-methyl-3-chloro-benzophenone. Dougherty (J.A.C.S., 1928, 50, 571) prepared benzophenone in good yield by heating o-benzoylbenzoic acid with finely divided copper or, better, with the copper salt of the acid at 260°. Shepard, Winslow and Johnson (J.A.C.S., 1930, 52, 2083) found that those halogeno-furoic acids resistant to decarboxylation by heat alone were readily decarboxylated by heating in quinoline with copper bronze.

In the synthesis of 3:4-benzphenanthrene Cook (J.C.S., 1931, 2524) found that the mixture of 1:2-benz-4-anthroic acid (II) and 3:4-benz-1-phenanthroic acid (III) formed by the Pschorr reaction on α-(2-naphthyl)-o-amino-cinnamic acid (I) was partly decarboxylated by vacuum sublimation at 230°, but neither the purified mixture nor the pure benzphenanthroic acid could be decarboxylated by sublimation even at 400° at atmospheric pressure. Complete elimination of carbon dioxide was obtained by heating the benzphenanthroic acid with Gatterman's copper powder at 400°.



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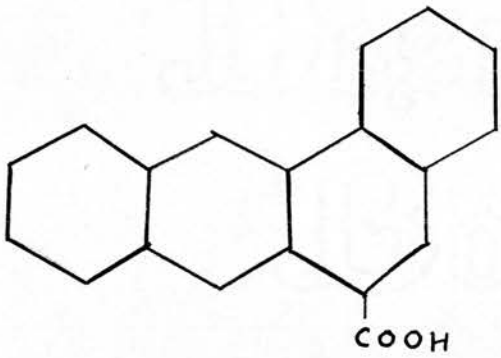
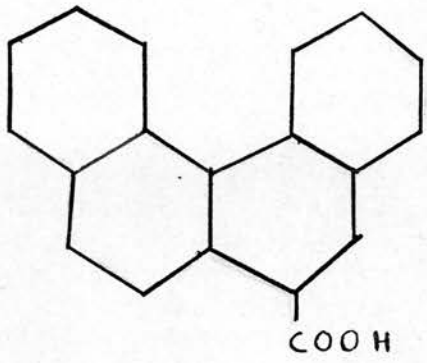


II



III

Davies, Heilbron and Irving (J.C.S., 1932, 2715) decarboxylated 3-nitro-7-methoxy-1-naphthoic acid by boiling in quinoline with copper bronze.

Reichstein, Grüssner and Zschokke (Helv. Chim. Acta., 1932, 15, 1066) used Adkins' copper chromite hydrogenation catalyst (J.A.C.S., 1931, 53, 1095) to decarboxylate 2-furyl-furan-3-carboxylic acid in boiling quinoline. Whittaker (Rec. Trav. Chim., 1933, 52, 354) used copper bronze in high-boiling tar bases to decarboxylate 5-bromo-furoic acid. Taylor and Crawford (J.C.S., 1934, 1130) prepared cis(iso)-stilbene from α-phenylcinnamic acid by heating in quinoline in presence of copper chromite at 210°. This method was also used by Alder and Windemuth (Ann., 1939, 543, 39) in decarboxylating α- and β-camphylic acids.

Copper bronze in boiling quinoline has also been used to decarboxylate the following acids, inter alia: nephthalic and 3:6-dinitronaphthalic (Rule and Brown, J.C.S., 1934, 171); benzanthrone carboxylic acids (Rule and Smith, J.C.S., 1937, 1096); 6-amino-4-hydroxy-quinaldinic acid (Kermack and Weatherhead, J.C.S., 1940, 1165).

Koelsch et al. (J.A.C.S., 1943, 65, 756, 989) have decarboxylated 3:4:6-triphenyl-2:5-dihydroxy-benzoic acid (triphenyl-gentisic acid) and 4:5-dinitro-1-naphthoic acid.

EXPERIMENTAL

PREPARATION OF MATERIALS.

4-Bromoacenaphthene.

(Anderson: Thesis, Edinburgh, 1938, 35.)

To a solution of 10 g. acenaphthene in 30 cc. ether an ethereal solution of bromine containing the theoretical amount of bromine for monobromination was added. The mixture was allowed to stand until the ether had evaporated and the oily solid was pressed between filter paper and recrystallised from methyl alcohol. Yields of 60% were obtained in several runs. M.p. 54-5°.

4-Acenaphthonitrile.

(Organic Syntheses, 21, 89.)

4-Bromoacenaphthene	39 g.
Cuprous Cyanide	18 g.
Pyridine	10 cc.

Refluxed in metal-bath at 215-225° for 18 hours.

Using the method of extraction with benzene-ether as given for α-naphthonitrile (Newman, Org. Synth., 21, 89) followed by removal of the solvent and recrystallisation of the residue from light petroleum (100-120°) only 9 g. of nitrile was obtained. The

residue from the benzene-ether extraction was boiled with conc. hydrochloric acid to remove copper and the residue extracted with boiling alcohol. Recrystallisation from light petroleum gave 7 g. nitrile m.p. 109-111° (lit. 111°).

4-Acenaphthoic acid.

The nitrile was hydrolysed neither by 50% sulphuric acid nor by a mixture of equal volumes of conc. sulphuric acid, glacial acetic acid and water. Hydrolysis was effected by boiling with 20% alcoholic potassium hydroxide. 10 g. 4-acenaphthonitrile were refluxed with 100 cc. 20% alcoholic potash for 20 hours. The solution was poured into diluted hydrochloric acid (1:1) and the solid filtered off. The solid was dissolved in sodium carbonate solution and the (small) insoluble residue removed by filtration. Acidification of this solution gave 11 g. of acid m.p. 218-9° (lit. 217°).

Cuprous Bromide.

Copper Sulphate pentahydrate	20 g.
Potassium Bromide	10 g.
Water	200 cc.

Sulphur dioxide was passed into the solution with gentle heating. The cuprous bromide formed as a white ppt., which was filtered off, washed with sulphurous acid and dried *in vacuo* over potassium hydroxide.

HALOGEN REMOVAL.

At first great difficulty was experienced in repeating the removal of bromine from 4-bromo-acenaphthene accomplished by Muir and Campbell. This was eventually shown to be due to the thermometer used registering a temperature very much higher than that actually reached in the sealed tube. Also the apparatus used did not allow of direct measurement of this temperature. The results of these early experiments will be given, since the main product obtained was 4-acenaphthonitrile and in one case 4-acenaphthoamide and since the results are in agreement with the mechanism of the reaction given in the introduction.

Unless otherwise stated, each experiment was carried out by heating in a sealed Carius tube (Jena blue- or red-line glass) the following substances:

4-Bromoacenaphthene	2.33 g. ($\frac{1}{100}$ mole)
Cuprous cyanide	0.95 g. ($\frac{1.1}{100}$ mole)
Pyridine	10 cc.
Water	2 cc.

The presence or absence of pressure in the tube after heating and the formation of copper bronze after heating were noted. The contents of each tube were then worked up as described.

Experiment 5.

The tube was heated for 18 hours at 280-300° (by thermometer, the temperature actually reached was certainly not more than 250°). The contents of the tube were poured into dilute hydrochloric acid and the solid which separated out was filtered off and washed with water. The solid was recrystallised from boiling alcohol (charcoal) which deposited yellowish-brown elongated prisms micro m.p. 91-100°; mixed m.p. with acenaphthene 70-90°. Recrystallisation from light petroleum gave yellow needles m.p. 108-112° (Sublimation). The substance was shown to contain nitrogen and analysis gave N = 7.71%: 4-Acenaphthonitrile, $C_{13}H_9N$, requires N = 7.82%.

The alcoholic filtrate was poured into water and the solid extracted with ether. The ether solution was dried over calcium chloride and the ether removed. The residue was insoluble in boiling light petroleum (80-100°). Recrystallisation from boiling xylene gave yellow elongated prisms micro m.p. 200-1°.

Analysis gave C = 78.5; H = 5.59%
calc. for 4-acenaphthoamide $C_{13}H_{11}ON$ C = 79.2; H = 5.58%

The m.p. of 4-acenaphthoamide is given in Beilstein as 198°.

It was not till a new thermometer was used that

success was attained, but it was realised that accurate control of the temperature was impossible owing to fluctuation in the gas pressure.

Experiment 12.

The tube was heated for 20 hours at 300°.

There was pressure on opening the tube and copper bronze was noticed. The contents of the tube were treated with dilute hydrochloric acid and filtered. The solid was shaken with sodium hydroxide solution and filtered. The filtrate, on acidification with hydrochloric acid gave no acid.

The solid was recrystallised from alcohol: 0.32 g. m.p. 77-92° were obtained; mixed m.p. with acenaphthene 77-93°. The picrate was prepared and after recrystallisation from alcohol melted at 157-162° (lit. 162°). The product is therefore acenaphthene.

The solid was recovered from the filtrate by pouring into water and this, along with the rest of the recrystallised material, was run through a short (4") column of alumina in benzene. Recrystallisation of the solid obtained by evaporating the benzene washings of the column from light petroleum (80-100°) gave 0.15 g. m.p. 91-5°; mixed m.p. with acenaphthene

91-5°. The filtrate from this was evaporated to dryness and the residue steam distilled. The solid was filtered off and recrystallised from alcohol and 0.12 g. of needles m.p. 92-4° were obtained. Total yield - 0.59 g. (38%).

Since the 4-bromoacenaphthene had been successfully converted to acenaphthene it was decided to investigate the question - Is the water necessary? Experiments 13 and 14 were therefore carried out. In 13 the tube contained the usual filling but in 14 the water was omitted. Both tubes were heated for 15 hours simultaneously in the furnace at 300°.

Experiment 13.

There was pressure in the tube. Copper bronze was noticed in the tube. The contents of the tube were treated with dilute hydrochloric acid in the usual way. When the tube was washed out with dilute acid there was effervescence which was probably due to carbonate formed in the reaction. The solid was filtered off and steam distilled. The solid was filtered. Recrystallisation from alcohol gave 0.66 g. m.p. 92-4°; mixed m.p. with acenaphthene 92-5° (42%).

Experiment 14 (water absent).

There was no pressure in this tube but copper bronze was noticed. The contents of the tube were worked up as above. The oily solid which was obtained in the steam distillation came over very much more slowly than the acenaphthene in Experiment 13. The distillate was extracted with ether, the ether layer separated and dried over calcium chloride, and the ether removed. The solid was dissolved in benzene and run through a short column of alumina in benzene. The solid obtained by evaporating the benzene eluates was recrystallised from light petroleum (100-120) and melted at 107-110°; mixed m.p. with 4-acenaphthonitrile 108-111°.

Experiment 15.

Decarboxylation of acenaphthoic acid

4-Acenaphthoic acid	2.00 g.
Pyridine	10 cc.
Water	2 cc.

Heated in sealed tube for 12 hours at 300°.

Pressure in tube. The contents of the tube were poured into dilute hydrochloric acid and filtered. The solid was shaken with dilute sodium carbonate and filtered. On acidification the filtrate yielded acenaphthoic acid. The residue was taken up in ether

and the ether solution extracted twice with sodium carbonate solution, the extracts being combined and the acid precipitated. This was shown to be 4-acenaphthoic acid by its m.p. 206-216° and mixed m.p. with 4-acenaphthoic acid 213-9°.

The ether was removed and the solid steam distilled. The distillate was extracted with ether, the ether layer separated and dried over calcium chloride, and the ether removed. Recrystallisation from light petroleum gave needles m.p. 92-4° mixed m.p. with acenaphthene 92-4°; 0.18 g.

The filtrate was evaporated to dryness and the picrate prepared in alcohol: 0.39 g. of picrate m.p. 160-2° was obtained; mixed m.p. with acenaphthene picrate 160-2°. Total yield of acenaphthene 0.32 g. (28%).

The tube used in this experiment had been used before in an experiment with cuprous cyanide and almost certainly contained a trace of copper, which, it has already been pointed out, has a catalytic effect in the decarboxylation of carboxylic acids.

At this stage of the investigation it was realised that the gas furnace used did not give a steady temperature and that the type of bomb did not permit of observation of the temperature actually reached inside

the bomb. Pending the arrival of a new furnace, further investigation was limited to studies on decarboxylation of various acids, and then attention was turned to the synthesis of phenylacetonitriles, reported in the second part of this thesis. Towards the end of the period during which this research was carried out, an electric Carius tube furnace was available. With this apparatus it was possible both to maintain a steady temperature for a long time and to compare the temperature shown by a thermometer inside the liner in which the tubes are placed and that shown by a thermometer kept in the furnace. The variation in temperature was found to be less than 10° and as all the experiments were started at six p.m. fluctuation of the mains voltage was expected to be at a minimum. A rheostat was found to be necessary for control of the temperature reached and all the experiments were carried out with the sliding contact finally on the same stud, though in the initial period of heating the resistance was cut down.

Experiment 126.

The tube was heated for 10 hours at 300°.

There was pressure in the tube and copper bronze was observed. The method of working up was modified.

The contents of the tube were filtered and the tube washed out twice with ether which was used to wash the solid on the filter. The ether solution was washed three times with dilute hydrochloric acid to remove pyridine and was then shaken with dilute sodium carbonate solution. The sodium carbonate solution on acidification gave a slight trace of acid (not investigated further). The ether was taken off and the residue distilled. The distillate was extracted with ether, the ether layer separated and dried over calcium chloride. On removal of the ether 1.21 g. of acenaphthene was obtained; m.p. 91-3°; mixed m.p. with acenaphthene 92-4°. Yield 78%.

Experiment 129.

4-Acenaphthonitrile	1.79 g.
Cuprous bromide	1.44 g.
Pyridine	10 cc.
Water	2 cc.

There was a vigorous reaction when the water was added. The mixture was heated in a sealed tube for 10 hours at 300°.

There was pressure in the tube and copper bronze was noticed. Needles had crystallised out in the pyridine and were shown to be acenaphthene. The contents of the tube were worked up as in Experiment 126. A slight trace of acid and 1.16 g. (75%) of acenaphthene,

m.p. 89-93° (mixed m.p. with acenaphthene 92-5°) were obtained.

Experiment 130.

4-Acenaphthoic acid	1.98 g.
Cuprous bromide	1.44 g.
Pyridine	10 cc.
Water	2 cc.

Heated in sealed tube for 10 hours at 300°.

There was pressure in the tube and copper bronze was noticed. Needles of acenaphthene were noticed. The contents were worked up in the same way as in 126 and 129. A trace of acid was obtained. 1.00 g. acenaphthene was obtained m.p. 91-4°, mixed m.p. 93-5° (65%).

Experiment 134.

Cuprous bromide	1.44 g.
Pyridine	10 cc.

Heated at 300° for 10 hours.

There was a considerable evolution of heat when the pyridine was added to the cuprous bromide. After heating the formation of copper bronze similar in appearance to that observed in the other experiments was noticed.

Experiment 135.

Cuprous cyanide	0.95 g.
Pyridine	10 cc.

Heated in sealed tube at 300° for 10 hours (along with Experiment 134).

A dull red deposit of copper was formed on the walls of the tube but this did not resemble the spangles of copper bronze formed in the previous experiment or of any of the halogen removal experiments.

DECARBOXYLATION.

It has already been shown that the removal of halogen in the modification of the Rosenmund-von Braun nitrile synthesis occurs by way of the nitrile, amide and acid. It was thought worth while to investigate the decarboxylation of various acids. While this investigation was by no means complete, the results obtained with the few acids available are of some interest.

α-Naphthoic acid.

Experiment 17.

α-Naphthoic acid	1.72 g.
Pyridine	10 cc.
Water	2 cc.

Heated in sealed tube for 12 hours at 300°. Pressure on opening.

The contents of the tube were worked up as follows:- The solution was treated with dil. hydrochloric acid and the solid which separated was taken up in ether. This solution was extracted four times with dilute sodium hydroxide. The extracts on acidification with conc. hydrochloric acid gave 1.10 g. (64%) of α-naphthoic acid. The ether solution was washed with water, dried over calcium chloride and the ether removed.

0.07 g. of a waxy compound m.p. 60-75°, mixed m.p. with naphthalene 66-79° was obtained. The picrate melted at 146-151°, mixed m.p. with naphthalene picrate 146-151°.

Experiment 30.

α-Naphthoic acid	1.72 g.
Pyridine	10 cc.
Copper Bronze	0.64 g.

Heated at 300° for 12 hours. Pressure on opening.

The contents of the tube were worked up as above. No acid was obtained on acidification of the sodium hydroxide extract. 0.80 g. of naphthalene (63%) m.p. and mixed m.p. with naphthalene 79-80° were obtained.

Naphthalic acid.

Experiment 18.

Naphthalic acid	2.16 g.
Pyridine	10 cc.
Water	2 cc.

Heated at 300° for 12 hours. Pressure on opening.

Contents of tube worked up as above. 1 g. of α-naphthoic acid was obtained (60%). 0.31 g. of naphthalene m.p. 76-79°, mixed m.p. with naphthalene 77-79° (24%).

β-Naphthoic acid.

Experiment 25.

β-Naphthoic acid	1.72 g.
Pyridine	10 cc.

Heated in sealed tube for 12 hours at 300°. No pressure on opening.

Contents of the tube worked up as above. 1.65 g. (96%) of β-naphthoic acid were recovered. There was no residue on evaporation of the ether solution.

Experiment 28.

β-Naphthoic acid	1.72 g.
Pyridine	10 cc.
Copper Bronze	0.64 g.

Heated in sealed tube for 12 hours at 300°. Pressure on opening. Contents of the tube worked up as above. No acid was obtained. 0.90 g. (70%) naphthalene m.p. 79-80°, mixed m.p. with naphthalene 78-80° was obtained.

Experiment 72.

β-Naphthoic acid	1.0 g.
Quinoline	2 cc.
Copper Bronze	1 g.

Heated in a test tube in a metal bath. Effervescence began when the temperature inside the tube reached 150°. The temperature was gradually raised to 220-230° and maintained there for ten minutes.

When the tube was cold ether was added and the copper filtered off. Any acid not decomposed was removed by shaking with dil. sodium carbonate. 0.21 g. (28%) of naphthalene m.p. 73-77°, mixed m.p. 75-78° was obtained.

o-Benzoylbenzoic acid.

Experiment 73.

o-Benzoylbenzoic acid	1.0 g.
Quinoline	2 cc.
Copper Bronze	1 g.

Heated in a test tube in a metal bath. Vigorous effervescence occurred at 220°. After five minutes at 220° the speed of evolution slowed down and the temperature was raised. The produce was worked up as for experiment 72. No acid was obtained. The product after removal of the ether was an oil which solidified on seeding with a minute crystal of benzophenone. Yield 0.5 g. (62%). The dinitrophenylhydrazone melted at 240-241°, mixed m.p. with benzophenone dinitrophenylhydrazone 240-241°.

Experiment 69.

o-Bromotoluene	10 g.
Tetralin	50 cc.
Palladium Black	0.4 5.

Refluxed with vigorous boiling under a coil condenser with counter-current flow for 27 hours. Hydrogen bromide was detected ten minutes after heating had commenced. The liquid was fractionated and 0.5 g. b.p. 109-111° was obtained. This was probably toluene.

SUMMARY AND DISCUSSION OF RESULTS.

SUMMARY OF RESULTS.

Acenaphthene has been obtained by heating 4-bromoacenaphthene with cuprous cyanide, pyridine and water at 300° for 12 hours, whereas in the absence of water only acenaphthonitrile was obtained, but no acenaphthene. Acenaphthene has also been obtained by heating 4-acenaphthonitrile, cuprous bromide, pyridine and water, and 4-acenaphthoic acid, cuprous bromide and pyridine for 12 hours at 300°. Various aromatic carboxylic acids have been decarboxylated by heating with copper bronze in pyridine at 300° and with copper bronze in boiling quinoline, while in absence of copper, decarboxylation, if it occurs, occurs only to a very small extent.

DISCUSSION OF RESULTS.

The modification of the Rosenmund-von Braun reaction has been studied and evidence has been obtained to confirm the mechanism put forward in the introduction. This can be given briefly as:

$$RBr + CuCN \longrightarrow RCN + CuBr \quad \ldots\ldots\ldots \quad (1)$$

$$RCN + H_2O \longrightarrow RCONH_2 \quad \ldots\ldots\ldots\ldots \quad (2)$$

$$RCONH_2 + H_2O \longrightarrow RCOOH + NH_3 \quad \ldots\ldots \quad (3)$$

$$RCOOH \longrightarrow RH + CO_2 \quad \ldots\ldots\ldots\ldots \quad (4)$$

The earlier, unsuccessful experiments showed that at a temperature less than 300° (probably about 250°) the main product was the nitrile, along with a small quantity of the amide. It is reasonable to assume that this reaction will also occur at 300° and perhaps the conversion to nitrile will be complete before the temperature inside the tube has reached 300°. It is obvious that the water is essential, as, without it, the only product identified was the nitrile, whereas in a parallel experiment heated for the same time and at the same temperature, acenaphthene was obtained.

In the final series of experiments, carried out in the electric furnace, it was shown that acenaphthene could be obtained in reasonable or good yield by heating 4-bromoacenaphthene, cuprous cyanide, pyridine and water, 4-acenaphthonitrile, cuprous bromide, pyridine and water, 4-acenaphthoic acid, cuprous bromide and pyridine at 300° for 10 hours.

In all these cases the tube was under greater pressure after heating than before, and there was evidence of the presence of carbonate, while, in absence of water and where the product obtained was the nitrile, there was no excess pressure in the tube on opening. In all cases where a temperature

of 300° had been reached, the formation of copper bronze was noticed, and formation of this was also obtained by heating cuprous bromide in pyridine at 300°, but not from cuprous cyanide in pyridine at 300°. This is confirmatory evidence for the first step in the mechanism. Muir and Campbell did not always obtain the hydrocarbon as the product of this reaction; in some cases, e.g. ϒ-bromonaphthalene, the product was an acid amide, viz. α-naphthoamide. It is probable in these cases that the amide was resistant to hydrolysis under the conditions used and the reaction could thus proceed no further.

It is noteworthy that the products obtained by Rosenmund in the original work were, in most cases, the acids. Rosenmund used cuprous cyanide dissolved in an aqueous solution of potassium cyanide as the reagent and heated the halogeno compound with this for periods of eight to twenty hours at temperatures of about 190-220°. At the temperatures used, it is probable that decarboxylation, if it occurs, is very slow, and therefore the main product to be expected is the acid.

It is unfortunate that time did not permit of a fuller investigation of this reaction, using various

simple and substituted halogeno-compounds. From the results already obtained the stage most likely to cause trouble is the hydrolysis of the amide to the acid, and it is possible that this might be overcome by using Rosenmund's original reagents and a temperature of 300°.

The catalytic effect of copper and copper compounds in the decarboxylation of carboxylic acids is confirmed by the results obtained. It is interesting to note that in absence of copper, α-naphthoic acid when heated with pyridine at 300° for 12 hours is decarboxylated to a small extent whereas β-naphthoic acid under the same conditions is not decarboxylated at all. This illustrates the well known difference in reactivity of the alpha and beta positions of the naphthalene nucleus.

The removal of halogen by palladium black and boiling tetralin from o-chloromandelonitrile benzoate and o-bromotoluene was rather unexpected. Kindler and Peschke (Ann. 1932, 497, 196) prepared p-chlorophenylpropionic acid from p-chlorocinnamic acid by refluxing with palladium black in boiling tetralin. The halogen was not removed in this case. Rosenmund and Schindler (Arch. Pharm. 1928, 266, 281) hydrogenated O-acetyl-o-chloromandelic acid to o-chloro-

phenylacetic acid with no loss of halogen. Cook and Reed (J.C.S., 1945, 395) have used palladium black and tetralin to dehalogenate 5-chloro-6-azachrysene and 5-chloro-1:2-dihydro-6-azachrysene (the latter compound being dehydrogenated as well).

SYNTHESIS OF PHENYLACETONITRILES AND PHENYLACETIC ACIDS.

INTRODUCTION.

In connection with research on the reaction between benzanthrone and substituted benzyl cyanides attention was drawn to the unsatisfactoriness of the methods available for the synthesis of these compounds. Many methods are recorded in the literature and this profusion indicates the need for a general method giving good yields. Below is a summary of the various methods which have been used.

(a) Cyanation of Benzyl Halides.

This is the textbook method for the preparation of phenylacetonitriles. The benzyl halide is refluxed with an alcoholic solution of potassium cyanide. While high yields have been claimed for the method (e.g. 60-90% for some halogeno-substituted compounds) (Wislicenus and Elvert, Ber. 1908, 41, 4121; Zimmerman, J. Pr. Chem., 1902 [2] 66, 377; Walther and Wetzlich, J. Pr. Chem., 1900 [2] 61, 187), the reaction is not generally applicable. In some cases the main product is a benzyl ether (cf. Edwards, J.C.S., 1926, 740) and in others the yields are reduced by polymerisation of the nitrile. Kindler and

Gehlhaar (Arch. Pharm., 1936, 274, 385) have used a modified method: the benzyl halide in benzene is stirred vigorously with an aqueous solution of potassium cyanide with heating under reflux. Even though good yields can be obtained, the method is obviously limited by the availability of the benzyl halides. The meta-substituted benzyl halides especially are not easily obtained.

The method of Kindler and Gehlhaar has been used by Bide and Wilkinson (J.S.C.I., 1945, 64, 84) in the cyanation of 3:4-dimethoxy-benzyl chloride, formed by chloromethylation of veratrole. The best yields were obtained when the crude product from the chloromethylation was submitted directly to cyanation.

It may be as well to remark here that this method has several drawbacks. There is the initial difficulty of preparing the benzyl halide in good yield. Chlorination of toluenes results in the formation of mixtures of benzyl and benzal chlorides; substitution may also occur in the nucleus. Side-chain chlorination can be effected without any nuclear chlorination occurring with sulphuryl chloride catalysed by benzoyl peroxide (cf. Kharasch et al., J.A.C.S., 1939, 61, 2142) but this method does not give a quantitative

yield of pure benzyl chloride. The meta substituted toluenes cannot be prepared directly, whereas the m-substituted aldehydes can be obtained from m-nitrobenzaldehyde, which can be obtained by nitration of benzaldehyde. In some cases the benzyl chlorides required have been prepared from the benzaldehydes by catalytic hydrogenation to the benzyl alcohol and conversion of this to the chloride. It is obvious that a method using the aldehyde as starting material will have an inherent advantage over this method.

(b) Synthesis from Mandelonitriles, etc.

Purgotti (Gazz., 1895, 25, I, 120) prepared phenylacetonitrile by the action of hydrazine hydrate on mandelonitrile in boiling alcohol.

$$Ph.CHOH.CN \xrightarrow{H_2N.NH_2} Ph.CH_2.CN$$

Czaplicki, Kostanecki and Lampe (Ber., 1909, 42, 828) prepared o-hydroxyphenylacetic acid by the action of boiling conc. hydriodic acid on o-methoxymandelonitrile, formed from salicylaldehyde methyl ether. This method was used by Pictet and Gams (Ber., 1909, 42, 2949) for the preparation of 3:4dihydroxyphenylacetic acid required as an intermediate in the synthesis of papaverine.

Stevens (J.C.S., 1927, 181) obtained a 75% yield

of 3:4-methylene dioxyphenylacetic acid from the mandelic acid by conversion to the corresponding α-bromophenylacetic acid by the action of anhydrous hydrogen bromide in glacial acetic acid followed by reduction with zinc dust, the bromo compound not being isolated. Hignett and Kay (J.S.C.I., 1935, 54, 98T) prepared phenylacetonitrile in 56% yield from mandelonitrile by conversion to the α-chlorophenylacetonitrile by thionyl chloride and reduction of this with zinc dust and acetic acid. This method has been used recently by Davies, Johnson and Piggott (J.C.S., 1945, 352) in the preparation of o-methoxyphenylacetonitrile (yield 65% based on aldehyde).

Zelinsky, Packendorff and Leder-Packendorff (Ber., 1934, 67B, 300) prepared phenylacetic acid in theoretical yield and phenylacetonitrile in 79% yield by the catalytic hydrogenation of mandelic acid and nitrile using a platinised charcoal catalyst activated by palladium. For preparation of the catalyst see Dewar and Read (J.S.C.I., 1936, 55, 347T).

Rosenmund and Schindler (Arch. Pharm., 1928, 266, 281) showed that O-acetyl-mandelic acids on catalytic hydrogenation in boiling tetralin with palladised barium sulphate gave phenylacetic acids.

$$R.CH(OAc).COOH \longrightarrow RCH_2COOH + CH_3COOH$$

Kindler and Peschke (Ann., 1932, 497, 193) had shown that hydroaromatic compounds such as tetralin could act as sources of hydrogen in hydrogenation with palladium black (cf. Linstead, J.C.S., 1937, 1146; 1940, 1127, 1131, 1139). These authors showed later (Arch. Pharm., 1933, 271, 431) that mandelonitrile benzoates refluxed in boiling tetralin with palladium black gave benzoic acid and the phenylacetonitrile.

$$R.CH(OBz).CN \longrightarrow R.CH_2CN + BzOH$$

The mandelonitrile benzoates required for this synthesis can be easily prepared by shaking a mixture of the aldehyde and benzoyl chloride with concentrated aqueous potassium cyanide (Francis and Davis, J.C.S., 1909, 95, 1403). Yields of 60-80% were obtained by Kindler and co-workers in the preparation of alkyl- and alkoxy- phenylacetonitriles. Benzoyl and acetyl mandelic esters were also hydrogenated in this manner to the phenylacetic esters (Kindler and Gehlhaar, Arch. Pharm., 1936, 274, 377).

Recently Kindler and co-workers have hydrogenated mandelic acids and their ethyl esters in glacial acetic acid with the addition of conc. sulphuric acid or perchloric acid in presence of palladium black as a

catalyst. The mandelic esters have also been obtained by catalytic hydrogenation of phenylglyoxalates (Ann., 1943, 554, 9; Chem. Abs., 1943, 37, 5383; A., 1944, II, 76; Ber., 1943, 76B, 308; Chem. Abs., 1943, 37, 5709; A., 1945, II, 53) prepared from alkylbenzenes and phenol ethers with ethoxalyl chloride and aluminium chloride. A similar method has been used by Blicke and Grier (J.A.C.S., 1943, 65, 1725) to prepare p-xenylacetic acid in 48% yield from diphenyl. In this case the reduction of the mandelic acid was effected by iodine and red phosphorus in acetic acid.

(c) Willgerodt Reaction.

This is a method for preparing phenylacetamides from acetophenones. The acetophenone is heated with yellow ammonium sulphide in a sealed tube or an autoclave at 200-220° for a few (5-6) hours (Willgerodt et al., Ber., 1887, 20, 2467; 1888, 21, 535; J. Pr. Chem., 1909 [2] 80, 183, 192; 1910 [2] 81, 74, 382; 1911 [2] 84, 387, etc.)

$$R.CO.CH_3 \xrightarrow{(NH_4)_2S_x} RCH_2.CONH_2$$

This is not the only reaction that can occur; the yield is often lowered by the formation of thiophens and reduction of the carbonyl group with formation of

ethylbenzenes. Modifications have been introduced to eliminate these difficulties. Fieser and Kilmer (J.A.C.S., 1940, 62, 1357) obtained only traces of α-naphthylacetamide when α-acetylnaphthalene was submitted to the Willgerodt reaction, whereas, when the ketone was heated with yellow ammonium sulphide and dioxane at a lower temperature (160°) in a sealed tube for a longer time, a 57% yield of α-naphthylacetic acid was obtained. When larger runs were made in an autoclave the yield was reduced. Schwenk and Bloch (J.A.C.S., 1942, 64, 3051) prepared the morpholides of various phenylacetic acids by refluxing the acetophenone, morpholine and sulphur, thus avoiding the use of sealed tubes or autoclaves. The acids could be obtained by hydrolysis with 10% potassium hydroxide. The yields varied considerably, the best being from acetophenone and the methoxy derivatives. In general, good yields of the morpholides of the arylthioacetic acids were obtained but the yields of acid from this were not good. The yield of p-bromophenylacetic acid was 10%.

(d) Arndt-Eistert Reaction.

(Bachmann and Struve, Organic Reactions, 1942, 1, 38.)

This reaction affords a method for converting an

acid to its next higher homologue or some simple derivative of this latter.

$$R.COOH \longrightarrow R.COCl \longrightarrow R.CO.CHN_2 \longrightarrow R.CH_2COOH$$

Yields of 40-60% are quoted for the preparation of various phenylacetic acids but each step in the reaction is rather troublesome to carry out. Two mols. diazomethane must be present for each mol. acid chloride. Formation of the diazoketone is often slow, especially with aromatic acids. Incomplete reaction results in a mixture of homologues difficult to separate. The final product may also be contaminated with silver salts.

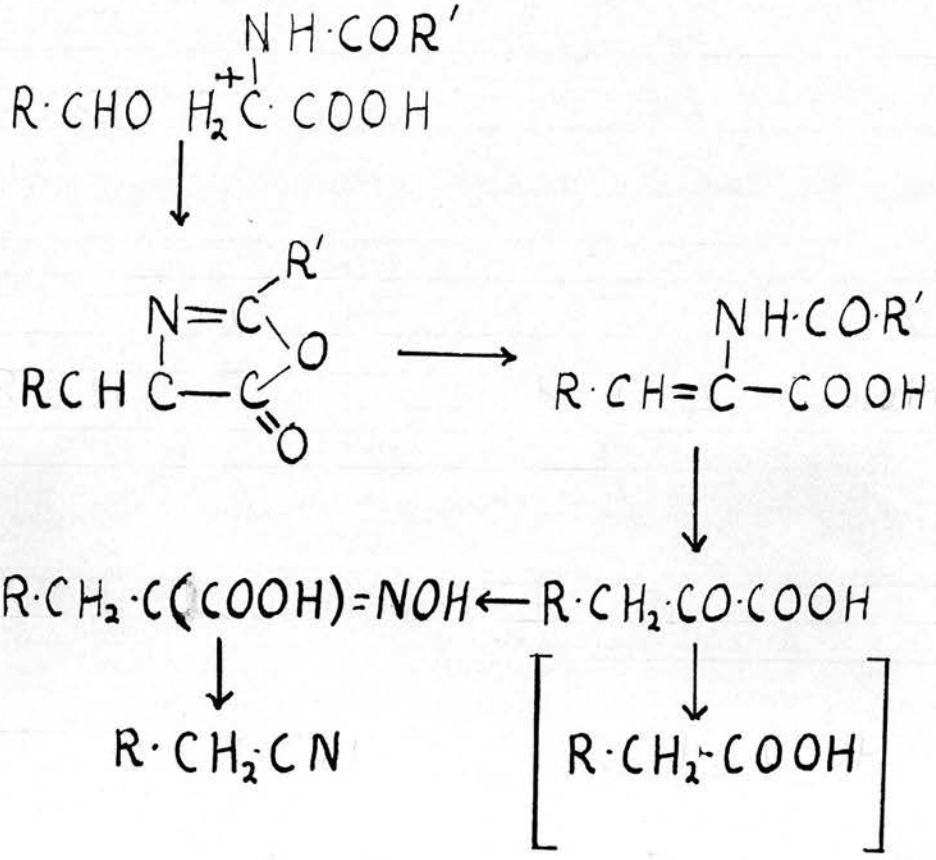
Fieser and Kilmer (loc. cit.) prepared o-bromophenylacetic acid in 62.5% yield (based on o-bromobenzoyl chloride).

(e) Azlactone Synthesis.

The Erlenmeyer azlactone synthesis has been used considerably in the preparation of phenylacetic acids (cf. Organic Reactions, 1942, 1, 231). An aromatic aldehyde is condensed with hippuric or aceturic acid in glacial acetic acid-acetic anhydride in the presence of anhydrous sodium acetate. The resulting azlactone is hydrolysed either with acid or alkali to a phenylpyruvic acid which can be oxidised in

alkaline solution to the phenylacetic acid by hydrogen peroxide. Aceturic acid is to be preferred in this reaction as, with hippuric acid, the benzoic acid formed in the hydrolysis of the azlactone is not always easily separated from the phenyl-pyruvic acid and the α-acetamido cinnamic acids are more easily hydrolysed. In some cases hydrolysis stops with the formation of the acetamido- or benzamido-cinnamic acid (cf. Gulland et al., J.C.S., 1931, 2889, 2901).

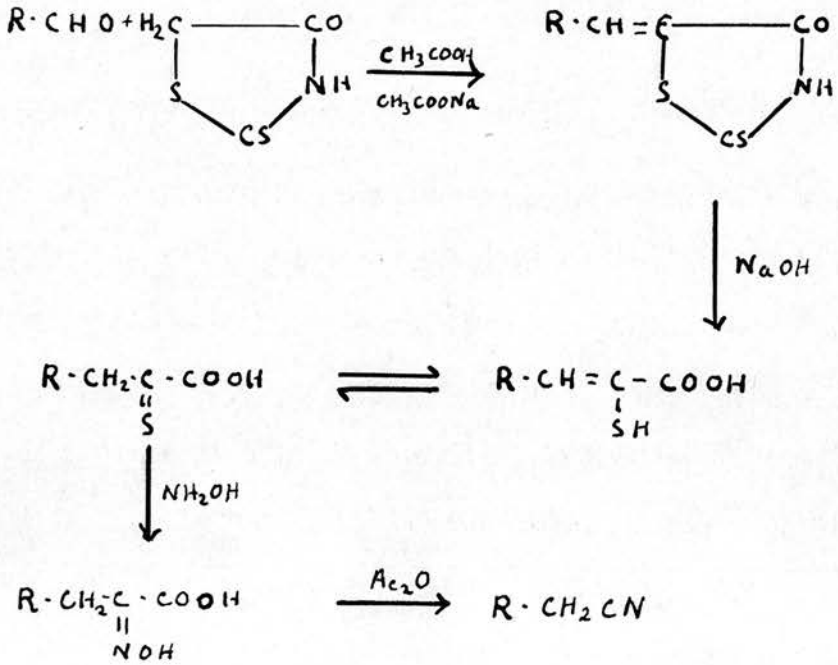
Edwards (J.C.S., 1926, 740) used a modification of this synthesis to prepare 3:4-methylenedioxy-phenylacetonitrile.



This method was also used by Niederl and Ziering (J.A.C.S., 1942, 64, 885) to prepare p-methoxy-, 3:4-dimethoxy- and 3:4-methylene-dioxy-phenylacetonitriles. The overall yields (based on aldehyde) were 15-20% using a five-stage synthesis (hydrolysis of the azlactone to the phenylpyruvic acid took two stages).

(f) Rhodanine Method.

The use of benzalrhodanines for the synthesis of phenylacetonitriles was suggested by Gränacher (Helv. Chim. Acta., 1922, 5, 610; 1923, 6, 458, 467). The synthesis takes four stages from the aldehyde.



Julian and Sturgis (J.A.C.S., 1935, 57, 1126) prepared p-methoxy-, 3:4 dimethoxy-, and 3:4-methylene-dioxy-phenylacetonitrile in good yield by this method. Plucker and Amstutz (J.A.C.S., 1940, 62, 1512) obtained a good yield of 2-furylacetonitrile from 2-furaldehyde in this way.

Attention was first drawn to this method by the review by Johnson (Organic Reactions, 1942, 1, 230) where the synthesis of 2-furylacetic acid in 73% overall yield from furfural by Plucker and Amstutz is quoted. The reviewer remarks: "It is difficult to find another series of reactions that gives such uncommonly good yields". This method seemed the most promising of all and it was decided to investigate its possibilities fully. The yields are very much superior to those obtained by other syntheses and, except for the rhodanine, no uncommon reagents or apparatus are required.

A summary of the yields obtained using the various methods quoted above shows the advantageous position of the rhodanine method as a general method.

(a) Cyanation of Benzyl Halides.

Wislicenus and Elvert	60-80%
Zimmermann	60%
Walther and Wetzlich	90%
Kindler and Gehlhaar	43-60% (on aldehyde)

(b) Mandelonitrile.

Purgotti	no yields quoted
Czaplicki, Kostanecki and Lampe	" " "
Pictet and Gams	" " "
Stevens	75%
Hignett and Kay	56%
Davies, Johnson and Piggott	65%
Zelinski et al.	79%
Rosenmund and Schindler	40-60%
Kindler et al. (Pd-tetralin)	60-80%

(c) Willgerodt

Fieser and Kilmer	57%
Schwenk and Bloch	10-70%

(d) Arndt-Eistert synthesis 40-60%

(e) Azlactone.

Edwards	no yield quoted
Niederl and Ziering	15-20%
Buck and Ide	28% (acid)

(J.A.C.S., 1932, 54, 3308)

(f) Rhodanine.

Julian and Sturgis	85%
Plucker and Amstutz	75%

PREPARATION OF ALDEHYDES.

p-Bromobenzaldehyde.

(Org. Synth. 18, 61.)

59 g. p-bromobenzaldehyde diacetate, m.p. 87-9° were obtained. By hydrolysis with alcoholic sulphuric acid there were obtained from 45 g. of this 20 g. of p-bromobenzaldehyde m.p. 55-7°. As a by-product in the oxidation, 24 g. p-bromobenzoic acid were also obtained.

m-Bromobenzaldehyde.

(Org. synth. 13, 30; 19, 86.)

Half quantities were used.

Yield 31 g. (51%).

The m-bromobenzaldehyde was obtained as a solid, a sample of which, on recrystallisation from light petroleum (40-60) by freezing out, melted at 22-3°. On analysis it gave 40.3% Br (calc. for C_7H_5OBr : Br 43.2%).

The 2:4-dinitrophenylhydrazone had not previously been prepared so it was made. It recrystallised from tetralin in clusters of orange prisms m.p. 254°.

Analysis $C_{13}H_9O_4N_4Br$ requires N = 15.4; fd. 15.3%.

m-Chlorobenzaldehyde.

(Org. Synth. 13, 28.)

Half quantities were used.

29 g. (63%) m-Chlorobenzaldehyde were obtained.

o-Bromobenzaldehyde.

(cf. Org. Synth., 18, 61)

o-Bromotoluene	62 g.
Glacial acetic acid	570 cc.
Acetic anhydride	565 cc.
Sulphuric acid (conc.)	85 cc.
Chromium trioxide	100 g.

The procedure was the same as that given in the reference for the para isomer. 69 g. (66%) of o-bromobenzaldehyde diacetate m.p. 83-5° were obtained. Brady, Cosson and Roper (J.C.S., 1925, 127, 2429) give 84-6° as the m.p. of this compound prepared in a similar way by chromic acid oxidation of o-bromotoluene in acetic acid-acetic anhydride solution. Brady hydrolysed the diacetate by refluxing with conc. hydrochloric acid, but this did not give a good yield, so alcoholic sulphuric acid was used.

o-Bromobenzaldehyde diacetate	45 g.
Alcohol	150 cc.
Water	100 cc.
Sulphuric acid (conc.)	10 cc.

The solution was refluxed for one hour and filtered through a fluted filter. The solution was poured into a large volume of water and the oil that separated was taken up in ether. The ether layer was separated, dried over calcium chloride, and the

ether removed. The oil was distilled *in vacuo*. B.p. 110-120°/12-14 mm. Yield 20 g. (69%).

PREPARATION OF p-BROMOPHENYLACETIC ACID.

(cf. Czaplicki, Kostanecki and Lampe, Ber., 1909, 42, 828.)

I. p-Bromomandelonitrile.

p-Bromobenzaldehyde	20 g.
Saturated sodium bisulphite	80 cc.
Alcohol	5 cc.

The aldehyde and the alcohol were mixed and shaken with the bisulphite solution (which must be freshly prepared). The bisulphite compound separated as a crystalline solid and was filtered off and washed with several portions of ice water. The bisulphite compound was made into a paste with water and a solution of 10 g. potassium cyanide in 20 cc. water added with stirring and the suspension stirred for two hours. The reaction mixture was extracted with ether, the ether layer separated and the ether removed. A waxy solid m.p. 60-70° was obtained. Yield 12.5 g.

A small quantity was twice recrystallised from benzene-light petroleum giving m.p. 78-9°.

Analysis: C_8H_6CNBr requires N = 6.61; fd. 6.39%.

II. p-Bromophenylacetic acid.

p-Bromomandelonitrile	11 g.
Hydriodic acid (d 1.94)	46 cc. (88 g.)

Refluxed for one hour. The reaction mixture was

poured into sodium bisulphite solution. The oil which separated was extracted with ether and a little solid which separated was filtered off. The ether layer was separated and washed first with more bisulphite and finally with water. The ether layer was extracted with three successive portions of sodium hydroxide solution until no more acid was left in the ether. On acidification of the combined extracts, 1.5 g. of acid m.p. 100-111° was obtained; Recrystallised from light petroleum, m.p. 111-4°; and then from aqueous alcohol, m.p. 111.5-114°.

Analysis: $C_8H_7O_2Br$ requires Br = 37.23; fd. 36.8%.

The ether layer, from which all the acid had been removed, was dried over calcium chloride and the ether removed. The solid which was left was recrystallised from benzene. Needles, m.p. 126-7°, were obtained.

Analysis: C 45.8; H 3.33; N 4.24; Br 36.0%.

No empirical formula could be found which agreed with these figures and also with its known properties. The compound was not investigated further. It cannot be p-bromophenylacetamide as this melts at 195°.

While it is possible to prepare phenylacetic acids by this method it is obviously not to be recommended for preparing these acids in good yield.

PREPARATION of o-BROMOPHENYLACETIC ACID.

(Fieser and Kilmer, J.A.C.S., 1940, 62, 1356.)

The diazomethane prepared from 20.6 g. nitrosomethylurea (Org. Synth. 15, 3) was diluted to 400 cc. with ether and dried over KOH. The ether solution was cooled in a freezing mixture and to it was added, during one hour, 11 g. o-bromobenzoyl chloride in ether with stirring and cooling to 0°. The mixture was allowed to stand one and a half days and the ether distilled off under reduced pressure, the temperature being kept below 30°. The oily residue was dissolved in dioxan and added to a suspension of 14 g. silver oxide in 700 cc. water containing 21 g. sodium thiosulphate at 60-65° during half an hour. Stirring was continued for a further half hour at 60-65°, 30 cc. 2N NaOH was added, and the silver oxide formed filtered off. The filtrate was washed with benzene and refiltered. The filtrate was acidified slowly with nitric acid and 5.36 g. of o-bromophenylacetic acid, m.p. 103-5° were obtained. The filtrate from this acid was made alkaline with NaOH and concentrated to 100 cc., filtered, and the filtrate acidified slowly with nitric acid: 1.59 g. acid, m.p. 95-100° were obtained.

Recrystallisation of the first crop from light petroleum gave m.p. 104.5-106°.

An attempt was made to prepare the m-bromophenylacetic acid from m-bromobenzoyl chloride and diasomethane in a similar way, but the product could not be purified.

It seems that, while the Arndt-Eistert synthesis is of great use in the preparation of homologues of acids *via* the acid chlorides, the yields are poor and the product may be a mixture of benzoic acid and its homologue.

PREPARATION OF PHENYLACETONITRILES FROM MANDELONITRILE BENZOATES.

I. Preparation of Palladium Black.

The palladium black catalyst was made by the method of Willstätter and Waldschmidt-Leitz (Ber., 1921, 54, 123).

II. Purification of Tetralin.

It was found that the best results were obtained if the tetralin was purified as follows. The tetralin was stirred at 30° with 80 cc. conc. sulphuric acid per litre; this was repeated until the sulphuric acid became only slightly yellow. The tetralin was separated, washed with water and steam distilled. The tetralin was separated from the distillate, dried over calcium chloride, refluxed over sodium and distilled from sodium. It was stored over sodium in a dark, well-stoppered bottle.

III. Preparation of p-Methoxy-phenylacetonitrile.

(a) p-Methoxy-mandelonitrile benzoate.

(cf. Francis and Davis, J.C.S., 1909, 95, 1403; Kindler and Peschke, Arch. Pharm., 1933, 271, 435.)

The method of preparation has been simplified. The oily nature of the product obtained using the procedure of Kindler and Gehlhaar was thought to be

due to free mandelonitrile. This was esterified by addition of a little more benzoyl chloride and sodium hydroxide. The rather tedious purification was eliminated and the product did not require recrystallisation.

Anisaldehyde	20 g.
Benzoyl chloride	22 g.
Sodium cyanide	15 g.
Water	20 cc.

The anisaldehyde was added to the aqueous sodium cyanide. The benzoyl chloride was added with vigorous stirring over 15 minutes and stirring was continued. The temperature was maintained at 35-40° by cooling with water if necessary. In about an hour the oil began to solidify and a few drops more benzoyl chloride were added and some dilute sodium hydroxide. Stirring was continued for ten more minutes. The pasty mass was triturated with dil. sodium hydroxide and filtered off. The solid was treated successively with dil. sodium hydroxide, water, saturated sodium bisulphite and finally with water. The yellowish solid was then triturated with a little alcohol and filtered and dried <u>in vacuo</u>. Yields of 29 and 36 g. (74 and 92%) were obtained in two runs. M.p. 64-5°.

(b) <u>p-Methoxy-phenylacetonitrile</u>.

p-Methoxy-mandelonitrile benzoate	30 g.
Tetralin	100 cc.
Palladium Black	0.8 g.

Refluxed for 45 minutes.

Following the procedure of Kindler and Peschke (loc. cit.) 6.5 g. (39%) of p-methoxy-phenylacetonitrile, b.p. 153-4°/14 mm., were obtained.

Attempted Preparation of o-Chlorophenylacetonitrile.

(a) o-Chloromandelonitrile Benzoate.

o-Chlorobenzaldehyde	20 g.
Sat'd sodium bisulphite	40 cc.
Sodium cyanide	14 g.
Water	20 cc.

The aldehyde was added to the sodium bisulphite and the mixture was stirred. After the bisulphite compound had formed the solution of sodium cyanide was added. The oil which formed was extracted with ether, the ether layer was separated and washed with saturated sodium bisulphite. The ether solution was dried and the ether removed.

The o-chloromandelonitrile obtained on evaporation of the ether was added gradually with stirring and cooling in water to a solution of 27 g. benzoyl chloride in 100 cc. pyridine and the solution was allowed to stand overnight. Water was added and the oil which separated was taken up in ether and the ether layer separated, washed with dil. hydrochloric acid to remove pyridine, then with dil. sodium carbonate and finally with water. The ether was dried over calcium chloride and the ether distilled off.

36 g. (93%) of oil was obtained. Analysis $C_{15}H_{10}O_2NCl$ requires N = 5.15; fd. 5.18%. After standing for a few weeks the oil solidified m.p. 55-6°.

(b) Hydrogenation of o-Chloro-mandelonitrile benzoate.

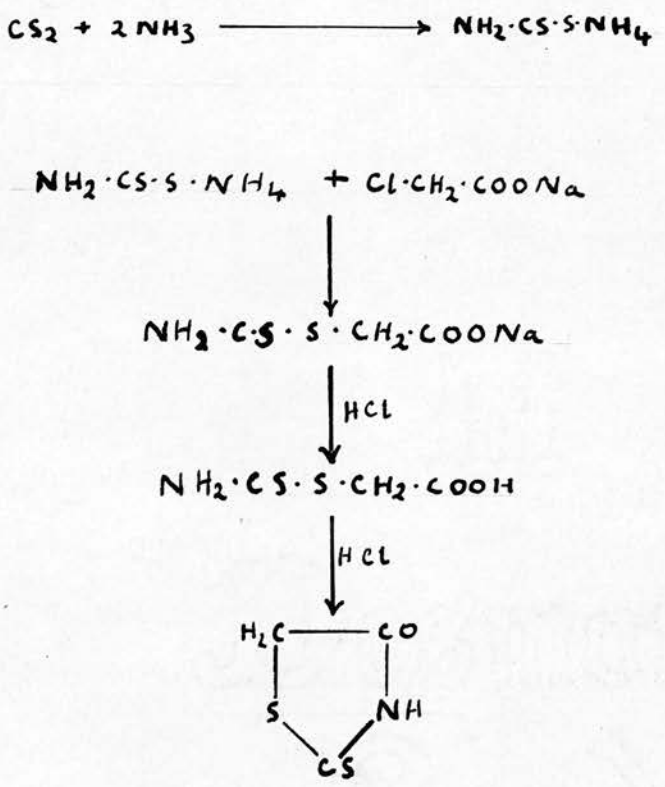
o-Chloro-mandelonitrile benzoate	17 g.
Tetralin	54 cc.
Palladium black	0.8 g.

Ten minutes after refluxing had started it was noticed that hydrochloric acid was being evolved. After 20 minutes half the liquid was removed but only 0.13 g. benzoic acid was obtained from this fraction. The rest was refluxed for 45 minutes in all and 0.77 g. benzoic acid was obtained from it. This fraction was distilled in vacuo but no o-chloro-phenylacetonitrile was obtained.

PREPARATION OF RHODANINE.

Julian and Sturgis (loc. cit.) described a method by which they claimed to have prepared large quantities of rhodanine in good yield. The first step was the preparation of ammonium dithiocarbamate by passing dry ammonia gas into a mixture of carbon disulphide, alcohol and ether with good cooling in a freezing mixture.

After 3½ hours the ammonium dithiocarbamate was filtered off and added to a solution of sodium chloracetate with stirring and good cooling. It is remarked that the colour of the solution should be "dark at first, gradually lightening and finally becoming a straw-yellow, if all has gone well". The resulting solution - containing thiocarbaminylthioglycollate, $H_2NCS.S.CH_2COO^-$ - was added to conc. hydrochloric acid at 80-90°, and rhodanine was obtained on cooling this solution.



Several attempts were made to prepare rhodanine by this method but, while some rhodanine was obtained in one or two cases from filtrates, the main product was generally a mixture, purification of which gave a bright yellow substance m.p. 170° (m.p. of rhodanine is 170°) which, however, contained no reactive methylene group, as it would not condense with aldehydes. This compound was later shown to be thiocarbonyl-bisthioglycollic acid, since it gave an aniline salt m.p. 118-9°; Holmberg (J. Pr. Chem., 1909 [2] 79, 267) quotes m.p. 119° for this salt. The thiocarbonyl-bisthioglycollic acid could have been formed only from ammonium trithiocarbonate $(NH_4)_2CS_3$, which must have

been formed by the action of ammonia on carbon disulphide. Search of the literature revealed that the action of alcoholic ammonia on carbon disulphide had been investigated by Zeise (Schweigger's J., 1824, 41, 98), and that this work had been further developed by Debus (Ann., 1850, 73, 26). Debus concluded: "Wenn Schwefelkohlenstoff, Ammoniak und wasserfreier Alkohol zusammengebracht werden, so beobachtet man nebeneinander zwei Processe, 1) die Bildung von Ammoniumsulfocarbonat und Schwefelcyanammonium, 2) die unmittelbare Vereinigung von 2 At. Ammoniak mit 2 At. Schwefelkohlenstoff zu sulfocarbaminsauren Ammoniumsulfuret. Concentrirte Flussigkeiten, eine Temperatur von 30 bis 40°, und Vorherrschen des Ammoniaks im Verhältnis zum Schwefelkohlenstoff, sind Bedingungen, die das Auftreten der unter 1) erwähnten Körper, wogegen verdünntere Auflösungen von Ammoniak in Alkohol und eine Temperatur von 10 bis 15° die Bildung der unter 2) angeführten Substanz vorzugsweise befördern."

There is an apparent discrepancy between the remark that a temperature of 30-40° is required for the formation of the trithiocarbonate and the instructions given by Mulder (J. Pr. Chem., 1868 [1] 103, 178) and by Freud and Bachrach (Ann., 1895, 285, 201)

for the preparation of ammonium dithiocarbamate, where a temperature of 30° is recommended. The explanation is probably to be found in the ammonia concentration, which experiments showed to be determinative. It is probable that the temperature given by Debus was that attained as a result of the reaction. The conclusions reached by Debus with regard to the effect of ammonia concentration on the product of the reaction were confirmed. As no simple test was available for distinguishing between ammonium dithiocarbamate and the trithiocarbonate, it was necessary to allow each product to react with chloracetate, allow to stand for about an hour and acidify with conc. hydrochloric acid in the cold. Ammonium dithiocarbamate gives thiocarbaminylthioglycollic acid $H_2N.CS.S.CH_2COOH$, and the trithiocarbonate thiocarbonyl-bis-thioglycollic acid $CS.(S.CH_2COOH)_2$; the former is pale yellow and melts at 137°, while the latter is bright yellow and melts at 172°. According to Clark (Handbook of Organic Analysis, 4th edn., p.264), sodium trithiocarbonate, obtained by the reaction of sodium hydroxide on carbon disulphide, gives a red colour with sodium nitroprusside. It was found that ammonium dithiocarbamate gave a blue colour deepening to violet

with sodium nitroprusside, and that the presence of some trithiocarbonate was shown by the appearance of a purple shade. The test is performed as follows:- A few mg. of the substance are dissolved in two drops 2N sodium hydroxide and two drops of a freshly prepared solution of sodium nitroprusside added. It was confirmed that the trithiocarbonate is much less stable than the dithiocarbamate in air.

After many trial experiments the most efficient method for preparing rhodanine was found to be the following.

Ammonia (from a cylinder of liquid ammonia) was passed fairly rapidly with stirring and cooling in ice-water into a mixture of 250 g. carbon disulphide, 200 cc. alcohol and 200 cc. ether, the temperature being kept at 5-15°, but not lower. After four hours 170 g. ammonium dithiocarbamate were obtained. This was added to a portion of the sodium chloracetate solution, prepared according to the instructions of Julian and Sturgis, equivalent to 146 g. chloracetic acid. A further 65 g. ammonium dithiocarbamate were obtained by passing ammonia into the filtrate for two hours. This was added to another portion of chloracetate solution equivalent to 56 g. chloracetic acid.

The solutions were combined and after standing for an hour were run into 302 cc. of conc. hydrochloric acid (10N) heated to 80-90° and maintained at 80-90° during the addition. On standing overnight rhodanine separated out. It was filtered off, washed with water and air dried. Yield: 125 g. (44%); m.p. 165-170°.

SYNTHESIS OF BROMO- AND CHLORO-PHENYLACETONITRILES BY RHODANINE METHOD.

Organic Reactions, 1942, 1, 229-230.

I. Preparation of Benzalrhodanines.

Molecular quantities of the aldehyde and rhodanine were dissolved in glacial acetic acid (5 cc. for each gram of aldehyde) with heating. Fused sodium acetate (twice the weight of rhodanine used) was then added and the reaction mixture refluxed in an oil-bath for half an hour. In some cases the benzalrhodanine was deposited soon after heating was commenced. When cold the benzalrhodanine was filtered off, washed with a little glacial acetic acid, washed well with water and dried at 70°. Yields were from 80-97%.

II. Preparation of Phenyl-thioketopyruvic Acids.

At first the method given by Julian and Sturgis (J.A.C.S., 1935, 57, 1126) was followed, using 15% sodium hydroxide (4 cc. per gram benzal-rhodanine). The crude acids obtained by this method were exceedingly impure and purification resulted in a great diminution in yield. The procedure finally adopted was cleavage with 8% sodium hydroxide (8 cc. per gram benzal-rhodanine) and heating in a water-bath at

50-55° instead of heating on the boiling water-bath. The suspension of the benzalrhodanine in the 8% sodium hydroxide was stirred well and heated in a water-bath at 50-55° until all or nearly all had gone into solution. The solution was filtered if necessary, cooled in an ice-salt freezing mixture and acidified rapidly with excess 3N hydrochloric acid with stirring. The stirring and cooling were continued for ten minutes, to ensure complete pptn. of the acid, which was filtered off, washed with water and dried *in vacuo* over calcium chloride.

All the common solvents were tried for purification but none gave a pure product in good yield. Gränacher (Helv. Chim. Acta., 1922, 5, 617) experienced some difficulty in recrystallising phenyl-thioketo-pyruvic acid from alcohol. He stressed the necessity of avoiding too high a temperature and recommended the addition of a trace of mineral acid. A good yield of a pure product was obtained by dissolving the crude dry acid in the minimum quantity of cold alcohol, filtering if necessary, and adding to the solution 1½-2 times its volume of cold water with stirring and shaking. After standing for 1-2 hours the acid was filtered off and dried *in vacuo* over calcium chloride.

In certain cases, viz., o-chloro-, p-chloro- and o-bromo- phenylthioketopyruvic acids the crude acids were found to be sufficiently pure for conversion to the oxime and it is quite probable that this also applies to the other three members but there was no opportunity to verify this.

As a rule runs were made with quantities of five or ten grams of the benzalrhodanine. While it is possible that larger quantities can be used it must be borne in mind that acidification must be rapid to avoid partial pptn. of the acid followed by re-solution, as this always leads to the formation of a sticky, gummy mass (cf. Julian and Sturgis, loc. cit.).

Yields were from 70-84%.

III. Preparation of α-Oximino-β-phenyl-propionic acids.

The phenylthioketopyruvic acids were converted to the corresponding oximino acids by refluxing with alcoholic hydroxylamine solution containing three molecular proportions of hydroxylamine. The alcoholic hydroxylamine solution was prepared by earlier workers by adding a strong aqueous solution of hydroxylamine hydrochloride to alcoholic sodium ethylate solution prepared from sodium equivalent to the hydroxylamine hydrochloride, and filtering off the

salt formed. This was found to be rather tedious and sodium acetate was used as base. While sodium acetate was found to be quite satisfactory for quantities of 1-2 grams it did not always give complete conversion with larger quantities and the acetic acid formed was a source of some trouble in working up the product. It was found that the sodium ethylate could be replaced by sodium hydroxide with no loss in yield. A standard alcoholic sodium hydroxide solution (2.5 N) containing 100 grams sodium hydroxide per litre was prepared. The hydroxylamine hydrochloride, dissolved in the minimum of warm water was added to enough of this solution to liberate the free hydroxylamine and alcohol added to bring the volume of the solution to ten cc. per gram of thioketo acid. The salt was filtered off, the thioketo acid dissolved in the solution and refluxed on the water bath until no more H_2S was evolved (about half an hour was generally required). The alcohol was removed by distillation under reduced pressure in the water-bath, the residue taken up in dilute sodium hydroxide solution, filtered and the filtrate acidified with conc. hydrochloric acid. The oximino acid was filtered off, washed well with water and dried <u>in vacuo</u> over

potassium hydroxide. The oximino acid obtained in this way was pure enough for conversion to the phenylacetonitrile without further purification.

Yields were from 80-100%.

IV. Preparation of phenylacetonitriles.

The crude oximino acid was added to acetic anhydride (4 cc. per gram oximino acid) and the mixture warmed gently under reflux. A vigorous reaction occurred and CO_2 was evolved, the flame being removed. When the vigorous reaction had ceased, the mixture was refluxed for ten minutes. The acetic anhydride was removed by distillation from the water-bath under reduced pressure. The residue was taken up in ether, the ether solution washed with sodium carbonate solution and then with water. The ether solution was dried over calcium chloride, the ether distilled off, and the residue distilled *in vacuo*.

Yields were from 55-88%.

Overall yields on aldehydes, 37-62%.

The phenylacetonitriles were hydrolysed to the corresponding phenylacetic acids by boiling with 50% sulphuric acid or 20% alcoholic KOH, the latter being preferred.

Below are given the details of the complete synthesis of the six chloro- and bromo-phenylacetonitriles. Usually small-scale runs were made for each stage in order to obtain just sufficient of the product for analysis, before proceeding to the next stage, and in some cases, particularly those of the thioketo-acids and oximino-acids, the methods used in these preliminary experiments differed from those finally adopted. In all such cases the identity of the product obtained by the later method with that of the analysed sample was shown by the method of mixed melting points.

Preparation of o-Chlorophenylacetonitrile.

I. o-Chlorobenzalrhodanine.

o-Chlorobenzaldehyde	10 g.
Rhodanine	10 g.
Glacial acetic acid	50 cc.
Sodium acetate (fused)	20 g.

Yield 18 g. (97%); m.p. 189-191°.

Recrystallisation from glacial acetic acid gave clusters of pale yellow needles m.p. 192° (micro).

Analysis: $C_{10}H_6ONCIS_2$ requires Cl = 13.87; fd. 12.80%.

Andreasch (Monats., 1928, 49, 132) prepared o-chlorobenzalrhodanine by heating equivalent amounts

of o-chlorobenzaldehyde and rhodanine in glacial acetic acid for one hour. He obtained flat brown-red needles m.p. 169° (from alcohol).

II. o-Chlorophenylthioketopyruvic acid.

o-Chlorobenzalrhodanine	5 g.
8% sodium hydroxine	40 cc.

Yield 3 g. (72%) m.p. 133-9°.

Recrystallisation of the thioketo acid from methyl alcohol gave prisms m.p. 134-5°.

Analysis: $C_9H_7O_2ClS$ requires S = 14.9; fd. 15.30%.

Recrystallisation from light petroleum (100-120) gave feathery needles m.p. 142.5-143.5° mixed m.p. with compound m.p. 134-5°, 139.5-141.5°.

Andreasch (loc. cit.) prepared o-chlorophenyl-thioketopyruvic acid by the action of baryta on o-chlorobenzal-rhodanine and on o-chlorophenyl-ν-phenyl-rhodanine. He obtained yellow needles m.p. 119-120°.

III. α-Oximino-β-(o-chlorophenyl)propionic acid.

o-Chlorophenylthioketopyruvic acid	3 g.
Hydroxylamine hydrochloride	3 g.
Water	2.5 cc.
2.5N Alcoholic sodium hydroxide	17 cc.
Alcohol	11 cc.

Yield 2.5 g. (83%) m.p. 146-8°.

Recrystallisation from aqueous alcohol raised the m.p. to 156°.

Analysis: $C_9H_8O_3NCl$ requires N = 6.56; fd. 6.78%.

IV. o-Chlorophenylacetonitrile.

α-Oximino-β-(o-chlorophenyl)-propionic acid	5.5 g.
Acetic anhydride	22 cc.

Yield 2.5 g. (64%); b.p. 123-5°/11 mm.

Analysis: C_8H_6NCl requires N = 9.25; fd. 9.75%.

V. o-Chlorophenylacetic acid.

Hydrolysis with 20% alcoholic potassium hydroxide gave needles, m.p. 93-5° (lit. 95°).

Recrystallisation from light petroleum (60-80) gave needles m.p. 93-4°.

Analysis: $C_8H_7O_2Cl$ requires Cl = 20.84; fd. 19.64%.

Preparation of m-Chlorophenylacetonitrile.

I. m-Chlorobenzalrhodanine.

m-Chlorobenzaldehyde	10 g.
Rhodanine	10 g.
Glacial acetic acid	50 cc.
Sodium acetate (fused)	20 g.

Refluxed for 10 minutes.

Yield 17 g. (93%); m.p. 230-3°.

Recrystallisation from glacial acetic acid gave pale yellow elongated prisms m.p. 233.5°.

Analysis: $C_{10}H_6ONClS_2$ required Cl = 13.87; Fd. 14.12%.

II. m-Chlorophenylthioketopyruvic acid.

m-Chlorobenzalrhodanine	10 g.
8% Sodium hydroxide	80 cc.

Stirred at 50-55°.

The acid was purified by dissolving in 56 cc. alcohol and precipitating with 84 cc. water.

Yield 7 g. (84%) m.p. 134-6°.

Recrystallisation from light petroleum gave pale straw needles m.p. 134°.

Analysis: $C_9H_7O_2ClS$ requires S = 14.90; Fd. 14.74%.

III. α-Oximino-β-(m-chlorophenyl)propionic acid.

m-Chlorophenylthioketopyruvic acid	7 g.
Hydroxylamine hydrochloride	7 g.
Water	5 cc.
2.5N Alcoholic sodium hydroxide	40 cc.
Alcohol	30 cc.

Yield 7 g. (100%) m.p. 145.5-148.5°.

Recrystallisation from benzene gave colourless needles m.p. 149.5°(d).

Analysis: $C_9H_8O_3NCl$ requires N = 6.56; Fd. 6.74%.

IV. m-Chlorophenylacetonitrile.

α-Oximino-β-(m-chlorophenyl) Propionic acid	7 g.
Acetic anydride	28 cc.

Yield 2.7 g. (55%) b.p. 134-6°/10 mm.

Analysis: C_8H_6NCl requires N = 9.25; Fd. 9.80%.

V. m-Chlorophenylacetic Acid.

Hydrolysis of a small quantity with 20% alcoholic KOH gave m-chlorophenylacetic acid m.p. 77°. Recrystallised from aqueous alcohol plates m.p. 77°. (Buck and Ide, J.A.C.S., 1932, 54, 3308, obtained plates from alcohol melting at 74° by the azlactone synthesis.)

Analysis: $C_8H_7O_2Cl$ requires Cl = 20.84; Fd. 21.12%.

Preparation of p-Chlorophenylacetonitrile.

I. p-Chlorobenzalrhodanine.

p-Chlorobenzaldehyde	5 g.
Rhodanine	5 g.
Glacial acetic acid	25 cc.
Sodium acetate (fused)	10 g.

Yield 8.5 g. (93%) m.p. 229-231°.

Recrystallised from glacial acetic acid; yellow needles m.p. 231-2°.

Analysis: $C_{10}H_6ONClS_2$ requires Cl = 13.87; Fd. 14.03%.

II. p-Chlorophenylthioketopyruvic acid.

p-Chlorobenzalrhodanine	5 g.
8% Sodium hydroxide	40 cc.

Stirred at 50-55°.

Yield 3.5 g. (84%) m.p. 164-7°.

Recrystallised from alcohol; yellow prisms m.p. 169-171° with resolidification and final melting at 202-4°.

Analysis: $C_9H_7O_2ClS$ requires S = 14.90; fd. 15.10%.

Gendelman (Monats., 1922, 43, 491) prepared this substance by the action of baryta on p-chlorobenzal-ν-phenylrhodanine and obtained pale yellow needles from alcohol, m.p. 157°.

III. α-Oximino-β-(p-chlorophenyl)propionic acid.

p-Chlorophenylthioketopyruvic acid	3.5 g.
Hydroxylamine hydrochloride	3.5 g.
Water	3 cc.
2.5N alcoholic NaOH	20 cc.
Alcohol	12 cc.

Yield 3.5 g. (100%) m.p. 155-6°.

Recrystallised from aqueous alcohol m.p. 170° (d).

An oxime, previously prepared, melted at 182° after recrystallisation from aqueous alcohol. Mixed m.p. with oxime of m.p. 170°, 170°(d).

Analysis of oxime of m.p. 182°: $C_9H_8O_3NCl$ requires N = 6.56; fd. 6.17%.

IV. p-Chlorophenylacetonitrile.

α-Oximino-β-(p-chlorophenyl)-propionic acid	7 g.
Acetic anhydride	28 cc.

Yield 4 g. (80%) b.p. 137-9°/12 mm. Solidified on cooling. Recrystallised by dissolving in light petroleum (40-60) and freezing out; colourless needles m.p. 31-2° (micro).

Analysis: C_8H_6NCl requires N = 9.25; fd. 9.50%.

V. p-Chlorophenylacetic acid.

Hydrolysis with 50% sulphuric acid gave the acid which was obtained as needles from light petroleum (80-100), m.p. 104-6° (lit. 105-6°).

Analysis: $C_8H_7O_2Cl$ requires Cl = 20.87; fd. 21.7%.

Preparation of o-Bromophenylacetonitrile.

I. o-Bromobenzalrhodanine.

o-Bromobenzaldehyde	10 g.
Rhodanine	8 g.
Glacial acetic acid	50 cc.
Sodium acetate (fused)	16 g.

Yield 13 g. (80%), m.p. 178-181°.

Recrystallised from glacialacetic acid: orange needles, m.p. 183.5°.

Analysis: $C_{10}H_6ONBrS_2$ requires Br = 26.68; fd. 22.64%.

Recrystallisation from ethyl acetate gave orange needles m.p. 184-5°. Analysis of this was also unsatisfactory.

Analysis: $C_{10}H_6ONBrS_2$ requires Br = 26.68; fd. 28.85%.

A satisfactory analysis for this compound could not be obtained; but satisfactory results were obtained in the other stages of the synthesis.

II. o-Bromophenylthioketopyruvic acid.

o-Bromobenzalrhodanine	5 g.
8% NaOH	40 cc.

Yield 3 g. (70%), m.p. 134-9°.

Recrystallised from light petroleum (100-120): lemon yellow elongated prisms m.p. 142-3°.

Analysis: $C_9H_7O_2BrS$ requires S = 12.36; fd. 11.27%.

III. α-Oximino-β-(o-bromophenyl)propionic acid.

o-Bromophenylthioketopyruvic acid	3 g.
Hydroxylamine hydrochloride	3 g.
Water	2.5 cc.
2.5N Alcoholic NaOH	17 cc.
Alcohol	11 cc.

Yield 3 g. (100%) m.p. 150°(d).

Recrystallised from benzene; fine white needles m.p. 150°(d).

Analysis: $C_9H_8O_3NBr$ requires N = 5.43; fd. 5.34%.

IV. o-Bromophenylacetonitrile.

α-Oximino-β-(o-bromophenyl)-propionic acid	7.5 g.
Acetic anhydride	30 cc.

Yield 5.0 g. (88%) b.p. 140-1°/13 mm.

Analysis: C_8H_6NBr requires N = 7.14; fd. 7.88%.

V. o-Bromophenylacetic acid.

A small quantity of the nitrile was hydrolysed with 20% alcoholic KOH and the acid obtained, after crystallisation from light petroleum (80-100) as needles m.p. 104-5°; mixed m.p. with o-bromophenylacetic acid previously prepared (v. s.) 104-105.5°.

Preparation of m-Bromophenylacetonitrile.

I. m-Bromobenzalrhodanine.

m-Bromobenzaldehyde	20 g.
Rhodanine	15 g.
Glacial acetic acid	100 cc.
Sodium acetate (fused	30 g.

Yield 29 g. (90%) m.p. 238°.

Recrystallised from glacial acetic acid, yellow

needles m.p. 238°.

Analysis: $C_{10}H_6ONBrS_2$ requires Br = 26.68; fd. 26.1%.

II. m-Bromophenylthioketopyruvic acid.

m-Bromobenzalrhodanine	20 g.
8% NaOH	160 cc.

Yield of crude thioketo acid 17 g. Purified by dissolving in 57 cc. alcohol and precipitating the acid by adding 90 cc. water. Yield 14 g. (81%) m.p. 132-4°.

Recrystallised from light petroleum (100-120) pale yellow needles m.p. 133-4°.

Analysis: $C_9H_7O_2BrS$ requires S = 12.36; fd. 12.70%.

III. α-Oximino-β-(m-bromophenyl)propionic acid.

m-Bromophenylthioketopyruvic acid	14 g.
Hydroxylamine hydrochloride	12 g.
Water	10 cc.
2.5N alcoholic NaOH	69 cc.
Alcohol	60 cc.

Yield 13 g. (93%) m.p. 151°.

This melting point was higher than that of a previously prepared sample which melted at 146.5°(d). However, the mixed m.p. was 151°(d).

The substance of m.p. 146.5° (crystallised from benzene) was analysed.

Analysis: $C_9H_8O_3NBr$ requires N = 5.43; fd. 5.47%.

IV. m-Bromophenylacetonitrile.

α-Oximino-β-(m-bromophenyl)-propionic acid	13 g.
Acetic anhydride	52 cc.

Yield 7 g. (70%) b.p. 145-7°/10 mm. Solidified on cooling. Recrystallised by freezing out from light petroleum (40-60), needles m.p. 27-8° (micro).

Analysis: C_8H_6NBr requires N = 7.14; fd. 7.52%.

V. m-Bromophenylacetic acid.

Hydrolysis of the crude nitrile with 20% alcoholic KOH gave an acid m.p. 80-95°. Recrystallisation from light petroleum (80-100) gave elongated prisms m.p. 94-7°. From water it was obtained as needles m.p. 102-3° (lit. 100°).

Analysis: $C_8H_7O_2Br$ requires Br = 37.23; fd. 37.00%.

Preparation of p-Bromophenylacetonitrile.

I. p-Bromobenzalrhodanine.

p-Bromobenzaldehyde	21 g.
Rhodanine	15 g.
Glacial acetic acid	105 cc.

Yield 28 g. (84%) m.p. 237-8°.

Recrystallised from glacial acetic acid yellow elongated prisms m.p. 237-8°.

Analysis: $C_{10}H_6ONBrS_2$ requires Br = 26.68; fd. 27.88%.

II. p-Bromophenylthioketopyruvic acid.

p-Bromobenzalrhodanine	20 g.
8% NaOH	160 cc.

Yield 13 g. (75%) (purified by dissolving in 255 cc. cold alcohol and ppting the acid with 282 cc. water) m.p. 165-180° approx.

All attempts to obtain a sharply melting specimen of this acid failed. All the products began to melt between 160-170° and melted over a considerable range even with rapid heating. The analytical sample was prepared by fractional pptn. by water from alcoholic solution.

Analysis: $C_9H_7O_2BrS$ requires S = 12.36; fd. 11.45%.

III. α-Oximino-β-(p-bromophenyl)propionic acid.

p-Bromophenylthioketopyruvic acid	13 g.
Hydroxylamine hydrochloride	11 g.
Water	10 cc.
2.5N alcoholic NaOH	60 cc.
Alcohol	70 cc.

Yield 11 g. (85%) m.p. 168-9°.

Recrystallised from toluene, colourless elongated

prisms m.p. 173.5°(d).

Analysis: $C_9H_8O_3NBr$ requires N = 5.43; fd. 5.28%.

IV. p-Bromophenylacetonitrile.

α-Oximino-β-(p-bromophenyl)-propionic acid	11 g.
Acetic anhydride	44 cc.

Yield 6 g. (72%) b.p. 152-6°/10-12 mm. m.p. 47-8°.

Recrystallised by freezing out from light petroleum (40-60), iridescent lamellae m.p. 48°.

Analysis: C_8H_6NBr requires N = 7.14; fd. 7.07%.

V. p-Bromophenylacetic acid.

Hydrolysis of a small quantity of the nitrile gave p-bromophenylacetic acid m.p. 113-5°; mixed m.p. with acid previously prepared 111-4°.

TABLE OF YIELDS.

Substituent	Stage of Synthesis				Overall yield
	I	II	III	IV	
o-Chloro	97	72	83	64	57%
m-Chloro	93	84	100	55	42%
p-Chloro	93	84	100	80	62%
o-Bromo	80	70	100	88	49%
m-Bromo	81	81	93	70	44%
p-Bromo	84	75	85	72	38%

DERIVATIVES OF PHENYLACETIC ACIDS.

The p-nitrobenzyl esters of all the halogenophenylacetic acids and the p-toluides that had not been prepared were made in the usual way, since they are useful for identification.

o-Chlorophenylacetic acid.

p-Nitrobenzyl ester: colourless prisms from alcohol, m.p. 70-71°. Analysis $C_{15}H_{12}O_4NCl$ requires N = 4.57; fd. 4.51%.

m-Chlorophenylacetic acid.

p-Nitrobenzyl ester: colourless micro crystals from alcohol, m.p. 74-75°. $C_{15}H_{12}O_4NCl$ requires N = 4.57; fd. 4.87%.

p-Toluidide: colourless crystals from dilute acetic acid, m.p. 138°. $C_{15}H_{14}ONCl$ requires N = 5.40; fd. 5.62%.

p-Chlorophenylacetic acid.

p-Nitrobenzyl ester: elongated prisms from alcohol, m.p. 117°. $C_{15}H_{12}O_4N$ Br requires N = 4.57; fd. 4.77%.

o-Bromophenylacetic acid.

p-Nitrobenzyl ester: plates from methylaclcohol, m.p. 74-75°. $C_{15}H_{12}O_4NBr$ requires N = 4.00;

fd. 4.40%.

p-Toluidide: elongated prisms from acetic acid, m.p. 183-184°. $C_{15}H_{14}ONBr$ requires N = 4.61; fd. 4.80%.

Ethyl ester: elongated prisms from light petroleum, m.p. 38-39°. $C_{10}H_{11}O_2Br$ requires Br = 32.9; fd. 33.1%.

m-Bromophenylacetic acid.

p-Nitrobenzyl ester: colourless micro crystals from methyl alcohol, m.p. 75-76°. $C_{15}H_{12}O_4NBr$ requires N = 4.00; fd. 4.30%.

p-Toluidide: colourless crystals from dilute acetic acid, m.p. 135°. $C_{15}H_{14}ONBr$ requires N = 4.62; fd. 4.75%.

p-Bromophenylacetic acid.

p-Nitrobenzyl ester: elongated prisms from alcohol, m.p. 128-129°. $C_{15}H_{12}O_4NBr$ requires N = 4.00; fd. 4.25%.

p-Toluidide: prisms from benzene, m.p. 203°. $C_{15}H_{14}ONBr$ requires N = 4.61; fd. 4.66%.

CATALYTIC HYDROGENATION OF MANDELIC ACID.

Many attempts were made to repeat Zelinsky's preparation of phenylacetic acid by hydrogenation of mandelic acid with a platinised charcoal catalyst activated by palladium. Zelinsky did not give details for the preparation of the catalyst.

Two platinised charcoal catalysts were prepared (Houben, Methoden der organischen Chemie, 3rd edn., pp. 324, 500); the first (p. 324) was very active in hydrogenating benzoin but the second was not effective for this until it had been heated in a stream of hydrogen. Neither would hydrogenate mandelic acid to phenylacetic acid even when palladium was added. One experiment will be described but the same negative result was obtained with all.

Experiment 53.

Mandelic acid	1.52 g.
Alcohol	50 cc.
10% Platinised charcoal	0.5 g.
Alcoholic palladium chloride (contains 0.025 g. palladium)	1 cc.

There was no significant drop in pressure on shaking in the hydrogenation apparatus for some hours with hydrogen at a pressure of 30 lbs. per sq. in. and the mandelic acid was recovered unchanged.

SUMMARY AND DISCUSSION OF RESULTS.

The six chloro- and bromo-phenylacetonitriles have been prepared in overall yields of 38-62% (on aldehyde) by the rhodanine method, a method found to be superior to all others tried. The directions given by Julian and Sturgis for the preparation of rhodanine were found to require considerable modification. Rhodanine could be obtained only in small amount by following these instructions but a reasonable yield was obtained by the modified method. A simple colour reaction is described which differentiates between ammonium dithiocarbamate and trithiocarbomate.

The yields of phenylacetonitriles obtained, while not so good as those claimed by either Julian and Sturgis or Plucker and Amstutz, nevertheless compare favourably with those obtained by other methods (see introduction).

The stage of the synthesis at which trouble is most likely to arise is the cleavage of the benzal-rhodanine by alkali. Previous workers have all emphasised the necessity of purifying the thioketo-pyruvic acid before conversion to the oxime, but most solvents used for recrystallisation resulted in very

large losses. It was found, however, that fractional pptn. from cold alcoholic solution with water gave a good yield of a product sufficiently pure for conversion to the oxime, especially if the cleavage were carried out with more dilute alkali (8% instead of 15%) and at a lower temperature (50-55° instead of 100°).

It was found later that the crude o- and p-chloro- and p-bromo- acids obtained by the action of 8% sodium hydroxide at 50-55° did not need purification before conversion to the oxime.

The method of Kindler and Peschke which looked so promising was found to be inapplicable as a general method in the halogeno-series as the halogen was removed and the catalytic activity of the palladium black in hydrogenolysis of the ester group poisoned. The method was found to give fairly good yields (not so good as those claimed) in the preparation of p-methoxyphenylacetonitrile, but the naphthalene, formed by dehydrogenation of the tetralin, cannot be separated completely from the nitrile by distillation.

Many attempts were made to repeat Zelinsky's work on hydrogenation of mandelic acid. Two different platinised charcoal catalysts were prepared, but, while

both were very active in hydrogenating benzoin, no hydrogenation occurred when mandelic acid was used. Zelinsky did not describe the preparation of the platinised charcoal catalyst in any of his papers, and it was only recently that a detailed reference to the preparation was discovered, in a paper by Dewar and Read (J.S.C.I., 1936, 55, 347T). This describes the preparation of a platinised charcoal catalyst for dehydrogenation and is the only reference that was discovered after a long search of the literature. The direct replacement of the hydroxyl group in mandelic acid and its esters by hydrogen has been accomplished by Kindler and co-workers (see introduction). Kindler ascribed this to the formation of molecular compounds between the mandelic acid and the sulphuric or perchloric acid added as promoter.

Simultaneous reduction and hydrolysis of mandelonitriles to the corresponding phenylacetic acid provides a fairly rapid way but the yields are poor. Hydriodic acid may react with other groups present in the molecule, thus limiting the usefulness of this method.

A comparative investigation of the azlactone synthesis could not be carried out owing to difficulty in

procuring glycine. If the work of Niederl and Ziering is taken as typical - and there seems to be no reason why it should not - there is a loss of over 50% in the preparation of the azlactone. Such a loss in the first stage of a multiple-stage synthesis immediately cuts down the maximum possible yield, however good the yields in the later stages may be. The question of expense also arises. It may be cheaper in the long run to use a more expensive starting material that gives better overall yields than those given by a relatively cheaper starting material. The yields obtained in later stages by these workers are good, e.g. 90% in the hydrolysis of the azlactone to the phenylpyruvic acid, a reaction in which side reactions tend to reduce the yields.

The Arndt-Eistert synthesis gives reasonably good yields of the acids but its usefulness is limited by the slow formation of the diazoketone and also by the difficulty in working with diazomethane. Again the product is the acid, or, if rearrangement of the diazoketone is carried out in ammoniacal solution, the amide. Where the nitrile is desired, an extra stage is added to the synthesis, thereby lowering the yield still further.

It may be concluded, therefore, that, while the rhodanine synthesis does not perhaps give such exceptionally good yields with halogeno-aldehydes as those obtained with alkoxy-benzaldehydes and fural, it does, nevertheless, provide a method for the preparation of phenylacetonitriles from benzaldehydes in reasonable yield. It should be stated here that the quantities generally used were about a tenth of those used by Julian and Sturgis, thus magnifying mechanical losses. Where only a small quantity of aldehyde is available this is probably the best method for converting it to the phenylacetonitrile or phenylacetic acid.

The p-nitrobenzyl esters and the p-toluides of the chloro- and bromo-phenylacetic acids have been prepared. The p-toluidides seem to be of most use in identification.

Finally, I wish to thank Dr Campbell for the helpful interest and advice during the course of this research.